PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07K 7/56, A61K 37/02 — A1

(11) International Publication Number: WO 93/21227

(43) International Publication Date: 28 October 1993 (28.10.93)

(21) International Application Number: PCT/EP93/00893

(22) International Filing Date: 13 April 1993 (13.04.93)

(30) Priority data:
FI92A000089 15 April 1992 (15.04.92) IT

(71) Applicants *(for all designated States except US)*: A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L.[IT/IT]; Via Sette Santi, 3, I-50131 Florence (IT). LABORATORI GUIDOTTI S.P.A. [IT/IT]; Via Trieste, 40, I-56126 Pisa (IT). MALESCI - ISTITUTO FARMACOBIOLOGICO S.P.A. [IT/IT]; Via Porpora, 22/24, I-50144 Florence (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : PAVONE, Vincenzo [IT/IT]; Viale Michelangelo, 56, I-80129 Napoli (IT). LOMBARDI, Angelina [IT/IT]; Corso Umberto I, 235, I-82034 Guardia Sanframondi (IT). PEDONE, Carlo [IT/IT]; Piazzetta Ascensione, 4, I-80121 Napoli (IT). MAGGI, Carlo, Alberto [IT/IT]; Via Michelazzi, 43, I-50141 Florence (IT). QUARTARA, Laura [IT/IT]; Viale Osimo, 385, I-52037 San Sepolcro (IT).

(74) Agent: GERVASI, Gemma; Notarbartolo & Gervasi S.r.l., Viale Bianca Maria, 33, I-20122 Milan (IT).

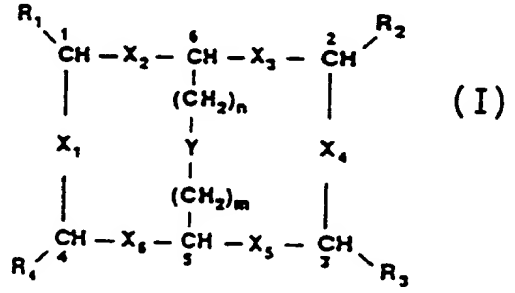
(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TACHYKININ ANTAGONIST TRICYCLIC COMPOUNDS, PREPARATION OF SAME AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS



(I)

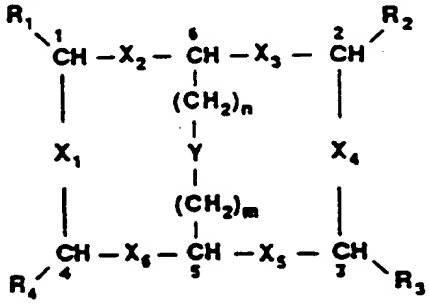
(57) Abstract

A description is given of tachykinin antagonist tricyclic compounds having general formula (I) where: X1, X2, X3, X4, X5, and X6, identical or different, are each selected out of the group consisting of -NR'-CO-, -CO-NR'-, where R' is H or C_{1-3}alkyl; Y is selected out of the group consisting of -CONR-, NRCO-, -OCO-, -COO-, $-CH_2$-NR-, -NR-CH_2-, -SS-, $-CH_2-CH_2$-, cis or trans -CH=CH-, where R is H or C_{1-3}alkyl; R1, R2, R3, and R4 are each a hydrophobic group; n and m, identical or different, are each a whole number from 1 to 4, the preparation of same and pharmaceutical compositions containing said compounds.

Tachiquinine antagonist tricyclic compounds, preparation of same and pharmaceutical compositions containing such compounds

Field of the invention

The present invention refers to compounds having general formula (I)



where:

X1, X2, X3, X4, X5, and X6, identical or different, are each selected out of the group consisting of -NR'-CO-, -CO-NR'-, where R' is H or C_{1-3}alkyl

Y is selected out of the group consisting of -CONR-, -NRCO-, -OCO-, -COO-, $-CH_2-NR-$, $-NR-CH_2-$, -SS-, $-CH_2-CH_2-$, cis or trans -CH=CH-, where R is H or C_{1-3}alkyl

R1, R2, R3, and R4 are a hydrophobic group

n and m, identical or different, are each a whole number from 1 to 4

the preparation of same and pharmaceutical compositions containing said compounds.

State of the art

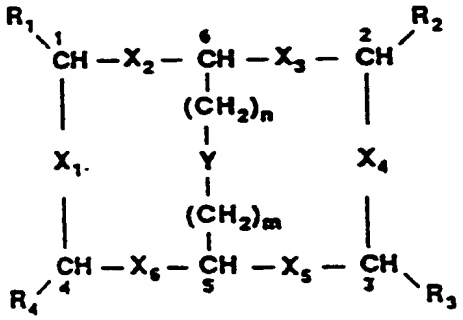
Tachyquinine antagonist compounds are known from literature. Among them, particularly interesting are the cyclic compounds [GB-A-2 216 529; McKnight, British Journal of Pharmacology, 104, 2 (1991); Gilon et al., Biopolymers, Vol. 31, 745-750 (1991); Harbeson et al.,

Peptides, Chemistry and Biology Proceedings 12th. APS, 124 (1992), Ed. Escom].

Although the chemical formula of the compounds considered herein is considerably different from that of the compounds already known, the pharmacological activity of the former is equal to or even higher than that of the latter. Therefore, the claimed compounds may be regarded as valid alternatives.

Detailed description of the invention

The present invention refers to new products of general formula (I)



where:

X1, X2, X3, X4, X5, and X6, identical or different, are each selected out of the group consisting of -NR'-CO-, -CO-NR'-, where R' is H or C_{1-3}alkyl

Y is selected out of the group consisting of -CONR-, -NRCO-, —OCO-, -COO-, $-CH_2$-NR-, -NR-CH_2-, -SS-, $-CH_2-CH_2$-, cis or trans —CH=CH-, where R is H or C_{1-3}alkyl

R1, R2, R3, and R4 are each a hydrophobic group

n and m, identical or different, are each a whole number from 1 to 4

the processes for the preparation of same and pharmaceutical

compositions containing such compounds.

As may be seen, the compounds as per formula (I) described above exhibit several chiral centres: it is understood that also the various enantiomers are an object of the present invention.

Hydrophobic groups R1, R2, R3, and R4 preferably consist of the side chains of hydrophobic amino acids, both natural and synthetic, or of the side chains of non-hydrophobic amino acids whose functional groups were derivatized in order to render them hydrophobic.

In particular, R1, R2, R3, and R4 may be selected out of the following groups:

a) linear or branched alkyl groups of the type C_nH_{2n+1} where n = 0, 1 to 4

b) linear or branched alkyl groups of the type C_nH_{2n}-U-W where n = 1 to 4; U = O, CO, COO, CONH, S, guanidine, NH and W = H, hydrophobic group containing 1 to 10 carbon atoms

c) $CH_2C_6H_3XY$ where X and Y, identical or different, are each H, halogen, OH, NH_2, CH_3 in an ortho or meta or para position of the benzene ring

d) $CH_2C_6H_4X$ where X = OR, SR, NHR, where R = hydrophobic group containing 1 to 10 carbon atoms

e) C_6H_3XY where X and Y, identical or different, are each H, halogen, OH, NH_2, CH_3 in the ortho or meta or para position of the benzene ring

f) $CH_2C_6H_{11}$

g) 1-methyl-naphthyl, 2-methyl-naphthyl

h) CH_2-imidazole

i) CH_2-indole

l) CH_2-(furanyl-3-yl)

m) CH_2-(pyridyl-3-yl)

n) CH_2-(imidazolyl-3-yl)

o) an eventually substituted, $-(CH_2)_3-$ group, which cyclizes with one of the two adjacent groups X to give the side chain of proline, hydroxyproline, dehydroproline.

In particular substituents R1, R2, R3, and R4 may be the side chains of hydrophobic natural amino acids selected out of the group consisting of: glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tyrosine, tryptophan, proline, histidine. R1, R2, R3, and R4 may also be the hydrophobic-derivatized side chains of non-hydrophobic amino acids selected out of the group consisting of: serine, threonine, cysteine, aspartic acid, asparagine, glutamic acid, glutamine, t-carboxyglutamic acid, arginine, ornithine, lysine.

R1, R2, R3, and R4 may also be the side chains of hydrophobic not natural amino acids selected out of the group consisting of: norleucine, norvaline, alloisoleucine, dehydroproline, hydroxyproline, cyclohexylglycine (Chg), α-amino-n-butyric acid (Aba), cyclohexylalanine (Cha), aminophenylbutyric acid (Pba), phenylalanines mono- and disubstituted in the ortho, meta, or para position of the aromatic ring with one or more of the following

groups: C_{1-10}alkyl, C_{1-10}alcoxyl, halogen, β-2-thienylalanine, β-3-thienylalanine, β-2-furanylalanine, β-3-furanylalanine, β-2-pyridylalanine, β-3-pyridylalanine, β-4-pyridylalanine, β-(1-naphthyl)alanine, β-(2-naphthyl)alanine, O-alkylated derivatives of serine, threonine, tyrosine, S-alkylated cysteine, S-alkylated homocysteine, alkylated lysine, alkylated ornithine, 2,3-diaminopropionic acid.

Out of the products as per formula (I) as defined above, particularly preferred are the products in which:

1) R1 = $-CH_2CH(CH_3)_2$

R2 = $-CH_2C_6H_5$

R3 = 

R4 = $-(CH_2)_2-SCH_3$

X1 = X2 = X3 = X4 = X5 = X6 = -CONH-

Y = -CONH-

wherein chiral carbon atoms exhibit L-configuration

2) Y = -NHCO-

the other substituents being as defined under point (1)

3) R4 = $-CH_2-C_6H_{11}$

the other substituents being as defined under point (1)

4) Y = -NHCO-

the other substituents being as defined under point (3)

5) R2 = R4 = $-CH_2-C_6H_5$

R1 = R3 = 

the other substituents being as defined under point (1)

6) Y = -NHCO-

the other substituents being as defined under point (5)

7) Y = -SS-

the other substituents being as defined under point (1)

8) Y = $-CH_2-CH_2-$

the other substituents being as defined under point (1)

9) Y = -CH=CH- (cis)

the other substituents being as defined under point (1)

10) Y = -CH=CH- (trans)

the other substituents being as defined under point (1)

11) m = n = 1

the other substituents being as defined under point (1)

12) m = 1, n = 2

the other substituents being as defined under point (1)

13) m = 1, n = 3

the other substituents being as defined under point (1)

14) m = 1, n = 4

the other substituents being as defined under point (1)

15) m = 2, n = 1

the other substituents being as defined under point (1)

16) m = 2, n = 2

the other substituents being as defined under point (1)

17) m = 2, n = 3

the other substituents being as defined under point (1)

18) m = 2, n = 4

the other substituents being as defined under point (1)

19) X1 = X2 = X3 = X4 = X5 = X6 = -NHCO-

the other substituents being as defined under point (1)

20) Y = -NHCO-

the other substituents being as defined under point (19)

21) R4 = $-CH_2-C_6H_{11}$

the other substituents being as defined under point (19)

22) Y = -NHCO-

the other substituents being as defined under point (15)

23) R2 = R4 = $-CH_2-C_6H_5$

R1 = R3 = 

the other substituents being as defined under point (19)

24) Y = -NHCO-

the other substituents being as defined under point (23)

25) Y = -SS-

the other substituents being as defined under point (19)

26) Y = $-CH_2-CH_2-$

the other substituents being as defined under point (19)

27) Y = -CH=CH- (cis)

the other substituents being as defined under point (19)

28) Y = -CH=CH- (trans)

the other substituents being as defined under point (19)

29) m = n = 1

the other substituents being as defined under point (19)

30) m = 2; n = 4

the other substituents being as defined under point (19)

31) the carbon atoms in positions 5 and 6 exhibit D-configuration

all substituents being as defined under point (1)

32) all chiral carbon atoms exhibit D-configuration

all substituents being as defined under point (1)

The compounds as per formula (I) covered by the invention can be prepared by known synthesis techniques, cf e.g. Schroeder et al., "The Peptides", Vol. 1, Academic Press, 1965; Bodansky et al., "Peptide Synthesis", Interscience Publishers, 1966; Barany and Merrifield, "The Peptides: Analysis, Synthesis, Biology", 2, Ch. 1, Academic Press, 1980.

The methods selected for the obtainment of the aforesaid products are the following:

i) synthesis in solution of the linear peptide chain by the coupling of suitably activated N-protected amino acids with an amino acid or a C-protected peptide chain, with intermediates isolation, followed by selective deprotection of C- and N-terminal chains, cyclization in organic polar solvents dilute solution, selective deprotection of the side chains and their cyclization in organic

polar solvents dilute solution (cf also Bodansky-Bodansky, "The procedure of peptide synthesis", Springer Verlag, 1984).

ii) peptide chain solid phase synthesis from C-terminal end to N-terminal end on an insoluble polymer support, cyclization in the solid phase of previously deprotected side chains, followed by detachment from the polymer support by hydrolysis in anhydrous hydrofluoric acid containing suitable scavengers or in trifluoracetic acid containing suitable scavengers and cyclization of monocyclic peptide in organic polar solvents dilute solution.

The process described above can alternatively consist of peptide chain solid phase synthesis from C-terminal end to N-terminal end on an insoluble polymer support, detachment from the polymer support by hydrolysis in anhydrous hydrofluoric acid containing suitable scavengers or in trifluoracetic acid containing suitable scavengers, cyclization of C-terminal and N-terminal ends in organic polar solvents dilute solution, deprotection of side chains and their cyclization in organic polar solvents dilute solution (cf the method described by Atherton et al. in Bioorganic Chemistry, 8, 351, 1979; by Merrifield in J.Am.Chem.Soc., 85, 2149-2154 (1963)). The first cyclization reaction can be carried out directly on the insoluble solid support (cf A.M. Felix et al., Int. J. Pep.Prot.Res., 31, 231, 1988; P. Rovero et al., Tetrahedron Letters, 32, 23, 2639 (1991), whereas the second cyclization can be carried out also in solution according to the procedures well known in the chemistry of peptide linkages (cf Kopple K.D., J. Pharmaceutical Sci., 61, 1345, 1972).

According to a particular method, the desired product may be obtained with PAM-resin (phenylacetoamidomethyl resin - A.R. Mitchell et al., J. Org. Chem., 43, 2845, 1978) functionalized with a Boc group protected amino acid at the N-terminal end. The amino acids directly bound to the resin are preferably the hydrophobic ones, such as Leu. After introduction of the other amino acids in the sequence, a first cyclization may be carried out reaching the side chains of the preferred aminoacids after their selective deprotection and activation. The monocyclic peptide can be removed by liquid hydrofluoric acid. The free peptide at N- and C-terminal ends can be further cyclized according to traditional synthesis methods.

The compounds as per formula (I) defined above proved to be more effective tachyquinine antagonists than other analogous antagonists; it follows that - compared with the known products - they may be administered at lower dose levels.

Therefore, they are suitable for the treatment of arthritis, asthma, inflammations, tumoral growth, gastrointestinal hypermotility, Huntington's disease, neuritis, neuralgia, migraine, hypertension, incontinence of urine, urticaria, carcinoid syndrome symptoms, influenza and cold.

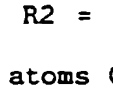
The compounds as per formula (I) covered by the invention are suitable for therapeutic administration to animals and man by the parenteral, oral, inhalatory, and sublingual ways, with

pharmacological effects matching the described properties. In case of parenteral administration (intravenous, intramuscular, intradermal), the compounds to be used are sterile solutions or freeze-dried preparations. In case of oral administration, preparations such as tablets, capsules and syrups are conveniently used. Suitable dosed ointments and creams are utilizable by the dermic way. In case of nasal instillation, inhalation, and sublingual administration, the compounds to be used are respectively aqueous solutions, aerosol preparations, or capsules.

Active ingredient doses in the aforesaid compositions range from 0.1 to 10 mg/kg body weight.

EXAMPLE 1

Preparation of cyclo(Met-Asp-Trp-Phe-Leu)

[Compound as per formula (I) where: Y = X1 = X2 = X3 = X4 = X5 = X6 = -NHCO-; m = n = 1; R1 = $-CH_2-CH(CH_3)_2$; R2 = $-CH_2-$  ; R3 = $-CH_2-C_6H_5$; R4 = $-CH_2-CH_2-SCH_3$; and carbon atoms C_1, C_2, C_3, C_4, C_5, C_6 have L-configuration]

Compound (1)

a) Synthesis of the monocyclic peptide having the following sequence: H-Met-Asp-Trp-Phe-Dpr-Leu-OH

0.625 Grams Boc-Leu-OCH_2-PAM resin (Applied BioSystem, USA, 0.8 meq/g), equal to 0.5 mmoles of amine groups, is fed an Applied BioSystem 430A (Foster City, CA, USA) semi-automatic peptide synthesis reactor. The Boc group is hydrolyzed with 33% TFA in DCM for 1.5 min. and with 50% TFA in DCM for 18.5 min.; then it is

neutralized with in DMF with 10% DIEA solution for 2 min. The following residues are made to react in the same order, in the quantities indicated in brackets: Boc-Dpr(Fmoc)-OH (0.852 g), Boc-Phe-OH (0.512 g), Boc-Trp(CHO)-OH (0.664 g), Boc-Asp(OFm)-OH (0.822 g).

The first acylation lasts 1 hour. The resin is washed and the reaction is ninhydrin-tested by the Kaiser method. In case of a negative response, the Boc group is hydrolyzed as described above, before the subsequent amino acid coupling. Acylation with Boc-Dpr(Fmoc)-OH is performed by adding an amino acid (2 mmoles) and PyBop (2 mmoles) solution in DMF to the deprotected resin. Boc-Phe-OH and Boc-Trp(CHO)-OH are coupled in the form of symmetric anhydride by dissolving 2 mmoles amino acid in 5 ml dichloromethane. The solution temperature is brought to 0°C and 1 ml of a 0.5 M solution of dicyclohexyl carbodiimide in dichloromethane is added. After 15 minutes, dicyclohexylurea is filtered and the resulting solution is added to the deprotected resin. Boc-Asp(OFm)-OH coupling is performed by adding the deprotected resin with an amino acid (2 mmoles) and HOBt (2 mmoles) solution in DMF; after 2 minutes, the suspension is added with a 0.5 M solution of DCC in DCM (4 ml). The fluorenyl groups on Asp and Dpr side chains are removed by treatment with a 20% (v/v) piperidine solution in DMF (15 ml twice for 3 and 7 min.). The condensation between β-amino and β-carboxyl groups is carried out with a 0.25 M solution of PyBop in DMF (3 equivalents)

in the presence of DIEA (6 equivalents) until negative response of the Kaiser Test.

Activated Boc-Met-OH (0.498 g) in the form of symmetric anhydride is coupled and, after terminal amine group deprotection, the formyl group of tryptophan is deprotected by treatment with 120 ml of 1 M solution of TMSiBr and 1 M solution of thioanisole in TFA in the presence of 1.2 ml m-cresol and 1.2 ml EDT. After 1 hour at 0°C, the solution is filtered, the resin washed with TFA and dried. The dry resin is placed in a Teflon reactor with 1 ml anisole and 1 ml dimethyl sulphide. The mixture temperature is brought to -50°C and 10 ml hydrofluoric acid is distilled therein; then the mixture is kept under stirring for 60 min. in an ice bath. Hydrofluoric acid is removed by nitrogen blowing. The raw product is dried under suction for about 2 hours, is washed with ethyl ether (15 ml twice), extracted in 50% acetic acid (15 ml three times), and filtered in a porous filter funnel to remove the exhaust resin. The resulting solution is diluted with water and freeze-dried. Finally, the peptide is purified by reversed phase chromatography and characterized by analytical HPLC on Varian LC Star 9010 Vydac C18 0.46 x 25 cm column with a linear acetonitrile gradient containing 0.1% (v/v) trifluoracetic acid (phase B) vs. 0.1% (v/v) aqueous trifluoracetic acid (phase A), as 5% to 70% phase B, in 50 min., at a rate of 1 ml/min., with 210 nm UV monitoring. Retention time (Rt) = 26.3'; chromatographic purity > 99%.

FAB-MS: $(M + H)^+ = 779$.

b) Cyclization of (a)

70 mg product (a) obtained as above is dissolved in 90 ml DMF. The solution is added with 47 mg PyBOP plus 20 µl DIEA. The resulting solution is kept under stirring at 0°C for 18 hours, then DMF is removed under vacuum and the resulting mixture freeze-dried. Compound (1) is purified by reversed phase liquid chromatography and characterized by analytical HPLC, on Varian LC Star 9010 Vydac C18 0.46 x 25 cm column with a linear acetonitrile gradient containing 0.1% (v/v) trifluoracetic acid (phase B) vs. 0.1% (v/v) aqueous trifluoracetic acid (phase A), as 5% to 70% phase B, in 50 min., at a rate of 1 ml/min., with 210 nm UV monitoring. Retention time (Rt) = 29.5'; chromatographic purity > 99%.

FAB-MS: $(M + H)^+ = 761$.

BIOLOGICAL ACTIVITY

The capacity of the products described in the present invention to interact with the neuroquinine A receptor as agonists or antagonists was assessed using a preparation characterized by the fact that the biological response produced by tachyquinines and correlated peptides was exclusively determined by the neuroquinine A receptor (receptor NK-2). The said preparation consisted of isolated rabbit pulmonary artery affected by a dose-dependent contraction brought about by tachyquinines (Rovero et al., Neuropeptides, 13, 263-270, 1989). The determination of the peptide activity in the test preparation was based on the use of an NKA concentration (3 nM)

causing a response equal to 45% of max. response. The peptides considered herein were added to the preparation in growing concentrations. Their activity was assessed as inhibition of response to NKA.

By way of example, compound 1 tested at a concentration of 1 M caused 100% inhibition of response to neuroquinine A in isolated rabbit pulmonary artery.

The capacity of the products described herein to interact with the P substance receptor (receptor NK-1) was assessed through an in vitro test, where the biological response produced by tachyquinines and correlated peptides was exclusively determined by the P substance receptor. The test preparation consisted of isolated guinea pig ileum affected by a dose-dependent contraction brought about by tachyquinines (Lee et al., Schmied. Arch. Pharmacol., 318, 281-287, 1982). The determination of the activity of the products as per the present invention in the test preparation was based on the use of an SP methyl ester concentration (10 nm) causing a response equal to 45% of max. response (S. Dion et al., Life Sci., 41, 2269-2278, 1987). The products considered herein were added to the preparation in growing concentrations. Their activity was assessed as inhibition of response to SP with satisfactory results.

By way of example, product 1 tested at a concentration of 10 mM caused 100% inhibition of response to SP methyl ester.

Abbreviations used

For the nomenclature and abbreviations of amino acids, reference is

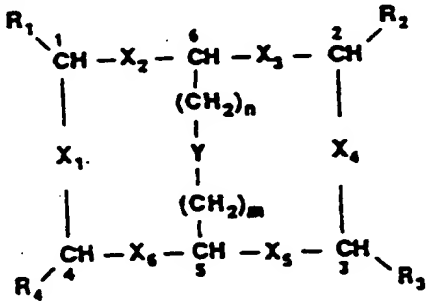
made to the rules issued by the IUPAC-IUB Joint Commission on Biochemical Nomenclature (Eur. J. Biochem., 1984, 138:9); unless otherwise specified, amino acids are considered in the L-configuration.

The other abbreviations used are the following:

Boc = tert-butyloxycarbonyl; DCM = dichloromethane; BOP = benzotriazolyl-N-oxytri(dimethylaminophosphonium) hexafluorophosphate, Dpr = 2,3-diaminopropionic acid; DCC = N-N'-dicyclohexyl carbodiimide; DCU = N-N' dicyclohexylurea; DIEA = diisopropylethylamine, DMF = N-N' dimethylformamide; EDT = ethandithiol; FAB-MS = fast atoms bombardment mass spectrometry; Fmoc = 9-fluorenylmethyloxycarbonyl, HOBt = 1-hydroxybenzotriazole; HPLC = high pressure liquid chromatography; iPrOH = isopropanol; PAM = phenylacetamidomethyl; NKA = neuroquinine A; SP = P substance; PIP = piperidine; TFA = trifluoracetic acid; For = formyl; Me = methyl; Ac = acetyl; Fm = fluorenylmethyl; PyBop = benzotriazole-1-yl-oxypyrrolidinephosphonium hexafluorophosphate.

CLAIMS

1. Products of general formula (I)



where:

X1, X2, X3, X4, X5, and X6, identical or different, are each selected out of the group consisting of -NR'-CO-, -CO-NR'-, where R' is chosen in the group consisting of H, C_{1-3}alkyl

Y is selected out of the group consisting of -CONR-, -NRCO-, -OCO-, -COO-, $-CH_2-NR-$, $-NR-CH_2-$, -SS-, $-CH_2-CH_2-$, cis or trans -CH=CH-, where R is chosen in the group consisting of H, C_{1-3}alkyl

R1, R2, R3, and R4 are each a hydrophobic group

n and m, identical or different, are each a whole number from 1 to 4.

2. The compounds of formula (I) according to claim 1 wherein R1, R2, R3, and R4 are selected out of the following groups:

a) linear or branched alkyl groups of the type C_nH_{2n+1} where n = 0, 1 to 4

b) linear or branched alkyl groups of the type C_nH_{2n}-U-W where n = 1 to 4; U = 0, CO, COO, CONH, S, guanidine, NH and W = H, hydrophobic group containing 1 to 10 carbon atoms

c) $CH_2C_6H_3XY$ where X and Y, identical or different, are each H,

halogen, OH, NH_2, CH_3 in the ortho or meta or para position of the benzene ring

d) $CH_2C_6H_4X$ where X = OR, SR, NHR, where R = hydrophobic group containing 1 to 10 carbon atoms

e) C_6H_3XY where X and Y, identical or different, are each H, halogen, OH, NH_2, CH_3 in the ortho or meta or para position of the benzene ring

f) $CH_2C_6H_{11}$

g) 1-methyl-naphthyl, 2-methyl-naphthyl

h) CH_2-imidazole

i) CH_2-indole

l) CH_2-(furanyl-3-yl)

m) CH_2-(pyridyl-3-yl)

n) CH_2-(imidazolyl-3-yl)

o) an eventually substituted, $-(CH_2)_3-$ group, which cyclizes with one of the two adjacent groups X to give the side chain of proline, hydroxyproline, dehydroproline

the other substituents being as defined in claim 1.

3. The compounds of formula (I) according to claim 2 wherein: R1, R2, R3, and R4 are the side chains of amino acids selected out of the group consisting of: glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tyrosine, tryptophan, proline, histidine, norleucine, norvaline, alloisoleucine, dehydroproline, hydroxyproline, cyclohexylglycine (Chg), α-amino-n-

butyric acid (Aba), cyclohexylalanine (Cha), aminophenylbutyric acid (Pba), phenylalanine mono- and disubstituted in the ortho, meta, or para position of the aromatic ring with one or more of the following groups: C_{1-10}alkyl, C_{1-10}alcoxyl, halogen, β-2-thienylalanine, β-3-thienylalanine, β-2-furanylalanine, β-3-furanylalanine, β-2-pyridylalanine, β-3-pyridylalanine, β-4-pyridylalanine, β-(1-naphthyl)alanine, β-(2-naphthyl)alanine, O-alkylated derivatives of serine, threonine, tyrosine, S-alkylated cysteine, S-alkylated homocysteine, alkylated lysine, alkylated ornithine, 2,3-diaminopropionic acid;

or they are the side chains of non-hydrophobic amino acids whose functional groups where derivatized in order to render them hydrophobic, selected out of the group consisting of: serine, threonine, cysteine, aspartic acid, asparagine, glutamic acid, glutamine, t-carboxyglutamic acid, arginine, ornithine, lysine.

4) The compounds of formula (I) according to claim 3 wherein:

R1 = $-CH_2CH(CH_3)_2$

R2 = $-CH_2C_6H_5$

R3 = $-CH_2$- 

R4 = $-(CH_2)_2-SCH_3$

X1 = X2 = X3 = X4 = X5 = X6 = -CONH-

Y = -CONH-

wherein chiral carbon atoms exhibit L-configuration.

5) The compounds of formula (I) according to claim 3 wherein:

Y = -NHCO-

the other substituents being as defined in claim 4.

6) The compounds of formula (I) according to claim 3 wherein:

R4 = $-CH_2-C_6H_{11}$

the other substituents being as defined in claim 4.

7) The compounds of formula (I) according to claim 3 wherein:

Y = -NHCO-

the other substituents being as defined in claim 6.

8) The compounds of formula (I) according to claim 3 wherein:

R2 = R4 = $-CH_2-C_6H_5$

R1 = R3 = $-CH_2-$ 

the other substituents being as defined in claim 4.

9) The compounds of formula (I) according to claim 3 wherein:

Y = -NHCO-

the other substituents being as defined in claim 8.

10) The compounds of formula (I) according to claim 3 wherein:

Y = -SS-

the other substituents being as defined in claim 4.

11) The compounds of formula (I) according to claim 3 wherein:

Y = $-CH_2-CH_2-$

the other substituents being as defined in claim 4.

12) The compounds of formula (I) according to claim 3 wherein:

Y = -CH=CH- (cis)

the other substituents being as defined in claim 4.

13) The compounds of formula (I) according to claim 3 wherein:

Y = -CH=CH- (trans)

the other substituents being as defined in claim 4.

14) The compounds of formula (I) according to claim 3 wherein:

Y = $-CH_2NH-$

the other substituents being as defined in claim 4.

15) The compounds of formula (I) according to claim 3 wherein:

Y = $-NHCH_2-$

the other substituents being as defined in claim 4.

16) The compounds of formula (I) according to claim 3 wherein:

m = n = 1

the other substituents being as defined in claim 4.

17) The compounds of formula (I) according to claim 3 wherein:

m = 2, n = 4

the other substituents being as defined in claim 4.

18) The compounds of formula (I) according to claim 3 wherein:

X1 = X2 = X3 = X4 = X5 = X6 = -NHCO-

the other substituents being as defined in claim 4.

19) The compounds of formula (I) according to claim 3 wherein:

Y = -NHCO-

the other substituents being as defined in claim 18.

20) The compounds of formula (I) according to claim 3 wherein:

R4 = $-CH_2-C_6H_{11}$

the other substituents being as defined in claim 18.

21) The compounds of formula (I) according to claim 3 wherein:

Y = -NHCO-

the other substituents being as defined in claim 20.

22) The compounds of formula (I) according to claim 3 wherein:

R2 = R4 = $-CH_2-C_6H_5$

R1 = R3 = $-CH_2-$ 

the other substituents being as defined in claim 18.

23) The compounds of formula (I) according to claim 3 wherein:

Y = -NHCO-

the other substituents being as defined in claim 22.

24) The compounds of formula (I) according to claim 3 wherein:

Y = -SS-

the other substituents being as defined in claim 18.

25) The compounds of formula (I) according to claim 3 wherein:

Y = $-CH_2-CH_2-$

the other substituents being as defined in claim 18.

26) The compounds of per formula (I) according to claim 3 wherein:

Y = -CH=CH- (cis)

the other substituents being as defined in claim 18.

27) The compounds of formula (I) according to claim 3 wherein:

Y = -CH=CH- (trans)

the other substituents being as defined in claim 18.

28) The compounds of formula (I) according to claim 3 wherein:

m = n = 1

the other substituents being as defined in claim 18.

29) The compounds of formula (I) according to claim 3 wherein:

m = 1; n = 2

the other substituents being as defined in claim 18.

30) The compounds of formula (I) according to claim 3 wherein:

m = 1; n = 3

the other substituents being as defined in claim 18.

31) The compounds of formula (I) according to claim 3 wherein:

m = 1; n = 4

the other substituents being as defined in claim 18.

32) The compounds of formula (I) according to claim 3 wherein:

m = 2; n = 1

the other substituents being as defined in claim 18.

33) The compounds of formula (I) according to claim 3 wherein:

m = 2; n = 3

the other substituents being as defined in claim 18.

34) The compounds of formula (I) according to claim 3 wherein:

m = 2; n = 2

the other substituents being as defined in claim 18.

35) The compounds of formula (I) according to claim 3 wherein:

m = 2; n = 4

the other substituents being as defined in claim 18.

36) The compounds of formula (I) according to claim 3 wherein the carbon atoms in positions 5 and 6 exhibit D-configuration, all substituents being as defined in claim 4.

37) The compounds of formula (I) according to claim 3 wherein all chiral carbon atoms exhibit D-configuration, all substituents being as defined in claim 4.

38) The pharmaceutical compositions containing compounds of formula (I) according to claim 1 mixed with suitable carriers.

39) The pharmaceutical compositions according to claim 38 for use as tachyquinine antagonists.

40) The compositions according to claim 38 for the treatment of arthritis, asthma, inflammations, tumoral growth, gastrointestinal hypermotility, Huntington's disease, neuritis, neuralgia, migraine, hypertension, incontinence of urine, urticaria, carcinoid syndrome symptoms, influenza and cold.

41) Method for the treatment of arthritis, asthma, inflammations, tumoral growth, gastrointestinal hypermotility, Huntington's disease, neuritis, neuralgia, migraine, hypertension, incontinence of urine, urticaria, carcinoid syndrome symptoms, influenza and cold, wherein the patient is administered 0.1 to 10 mg/kg active ingredient consisting of products of formula (I) according to claim 1.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
	claim 1. --	
A	Chemical Abstracts, vol. 116, no. 3, issued 1992, January 20 (Columbus, Ohio, U.S.A), A.T. McKNIGHT et al. "Pharmacological specificity of novel, synthetic, cyclic peptides as antagonists at tachykinin receptors", page 115-6, column 2, abstract no. 16246j, Br. J. Pharmacol. 1991, 104(2), 355-60, (Eng.). ----	1-40

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/00893

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC^5: C 07 K 7/56,A 61 K 37/02

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
IPC^5	C 07 K 7/00,C 07 K 15/00,C 12 P 21/00,C 12 N 5/00, C 12 N 15/00,A 61 K 37/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
P,A	Chemical Abstracts, vol. 117, no. 11, issued 1992, September 14 (Columbus, Ohio, U.S.A), S.L. HARBESON et al. "Cyclic psi(CH2NR)peptide neurokinin A antagonists; structure--activity and conformational studies", page 116, column 1, the abstract no. 104416r, Pept.: Chem. Biol., Proc. Am. Pept. Symp., 12th 1991, (Pub. 1992), 124-5, (Eng.). --	1-40
A	GB, A, 2 216 529 (MERCK SHARP & DOHME LTD.) 11 October 1989 (11.10.89), abstract. --	1-40
A	DE, A1, 3 915 361 (MERCK PATENT GMBH) 11 May 1989 (11.05.89),	1-40

* Special categories of cited documents: **

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
09 August 1993	27 -08- 1993
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCHARF e.h.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 93/00893

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 41
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 41 is considered to be a method for treatment of the human or animal body by therapy and is subject matter which the International Searching Authority is not required to search under Article 17(2)(a)(i) and Rule 39(iv).

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANHANG ANNEX ANNEXE

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

to the International Search Report to the International Patent Application No.

au rapport de recherche international relatif à la demande de brevet international n°

PCT/EP 93/00893 SAE 73380

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
GB A 2216529		GB A0 8807246	27-04-88
		GB A0 8905977	26-04-89
		GB A1 2216529	11-10-89
		GB B2 2216529	01-05-91
DE A1 3915361	15-11-90	AU A1 54808/90	15-11-90
		CA AA 2016355	11-11-90
		EP A1 401507	12-12-90
		HU A0 903011	28-09-90
		HU A2 56382	28-08-91
		JP A2 3002197	08-01-91
		ZA A 9003627	27-02-91